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Polycystic ovary syndrome: pathophysiology and therapeutic opportunities

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ABSTRACT

Polycystic ovary syndrome is characterised by excessive levels of androgens and ovulatory dysfunction, and is a common endocrine disorder in women of reproductive age. Polycystic ovary syndrome arises as a result of polygenic susceptibility in combination with environmental influences that might include epigenetic alterations and in utero programming. In addition to the well recognised clinical manifestations of hyperandrogenism and ovulatory dysfunction, women with polycystic ovary syndrome have an increased risk of adverse mental health outcomes, pregnancy complications, and cardiometabolic disease. Unlicensed treatments have limited efficacy, mostly because drug development has been hampered by an incomplete understanding of the underlying pathophysiological processes. Advances in genetics, metabolomics, and adipocyte biology have improved our understanding of key changes in neuroendocrine, enteroendocrine, and steroidogenic pathways, including increased gonadotrophin releasing hormone pulsatility, androgen excess, insulin resistance, and changes in the gut microbiome. Many patients with polycystic ovary syndrome have high levels of 11-oxygenated androgens, with high androgenic potency, that might mediate metabolic risk. These advances have prompted the development of new treatments, including those that target the neurokinin-kisspeptin axis upstream of gonadotrophin releasing hormone, with the potential to lessen adverse clinical sequelae and improve patient outcomes.

Introduction

Polycystic ovary syndrome is a common metabolic and reproductive disorder characterised variably by high levels of androgens, insulin resistance, and ovulatory dysfunction, with not all patients affected by these three parameters. These changes manifest as hyperandrogenism (hirsutism, acne, or scalp hair loss, or a combination of these), oligomenorrhoea or amenorrhoea, and morphological features of polycystic ovaries on ultrasound. Long recognised as a reproductive disorder, polycystic ovary syndrome is now also established as a metabolic condition associated with long term health risks, including type 2 diabetes and cardiovascular disease.[1] Adverse mental health outcomes and reduced quality of life have also been reported.[1] Polycystic ovary syndrome is therefore associated with substantial healthcare costs and resource utilisation. International surveys report a high level of dissatisfaction with care,[2] not least because current treatments are often only modestly effective in alleviating symptoms and minimising long term risks. International guidelines recognise the low quality of evidence and the critical need for better research.[3]

An improved understanding of the pathogenesis of the disease might result in the development of new treatments and better patient outcomes. Recent studies have advanced our understanding of these pathophysiological processes. Neuroendocrine dysregulation leads to abnormal high frequency pulsatile secretion of gonadotrophin releasing hormone, and hypothalamic kisspeptin, neurokinin B, and dynorphin A neurons (so-called KNDy neurons) are integral regulators of this process.[4] Although increased production of ovarian and adrenal androgens contribute to hyperandrogenism, peripherally generated 11-oxygenated androgens are emerging as important predictors of metabolic risk.[5 6] Together with advances in our understanding of adipocyte biology, insulin resistance, the gut microbiome, and insights from genome-wide association studies, these studies could improve our understanding of the pathogenesis of this disease. New treatments based on these observations are now in various stages of preclinical or clinical development.

This review outlines our current understanding of the key pathophysiological processes in polycystic ovary syndrome. We discuss the significance of new research into neuroendocrine dysfunction, disrupted steroidogenesis, and changes in adipocyte biology, and the potential implications for the diagnosis and management of polycystic ovary syndrome. Finally, we consider the benefits and limitations of current drug treatments, along with a review of the evidence for emerging drug treatments.

Epidemiology

Polycystic ovary syndrome is a common endocrine disorder in women of reproductive age,[7] with a prevalence of 4-21% depending on the diagnostic criteria used.[8] A systematic review of 13 studies found a slightly higher estimate of the prevalence in black and Middle-Eastern than in Chinese and white populations,[9] although inconsistencies in diagnostic criteria and recruitment methods make comparisons between ethnic groups challenging.[10] The global disease burden seems to be increasing at a high rate. In 2019, an age standardised point prevalence of 1677.8 per 100 000 and an annual incidence of 59.8 per 100 000 population were reported based on data

from 204 countries, representing increases of 30.4% and 29.5%, respectively, since 1990.[11] The rising incidence, and accompanying morbidity,[11] emphasises the importance of recognising polycystic ovary syndrome as an international public health priority.

Sources and selection criteria

We searched PubMed, Medline, and Embase from 1 January 2010 to 28 February 2023 for articles in the English language, with the search terms: "polycystic ovary syndrome," "polycystic ovarian syndrome," "PCOS," "aetiology," "etiology," "cause," "pathogenesis," and "pathophysiology." We excluded articles on endocrine conditions that might lead to secondary polycystic ovary syndrome, including acromegaly, androgen secreting tumours, congenital adrenal hyperplasia, and Cushing's syndrome. To identify registered clinical trials, we searched ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials (CENTRAL), and the International Standard Randomised Controlled Trial Number (ISRCTN) registry with the search terms "PCOS," "polycystic ovary syndrome," and "polycystic ovarian syndrome." We prioritised large scale, randomised controlled trials and systematic reviews. We also included relevant articles identified from reference lists of retrieved articles.

Pathogenesis

Neuroendocrine disruption

Polycystic ovary syndrome is characterised by increased pulse frequency of gonadotrophin releasing hormone and reduced negative feedback from sex steroids at the level of the hypothalamus.[4 12] Gonadotrophin releasing hormone is released from neurons in the hypothalamic infundibular nucleus in a pulsatile manner, resulting in increased secretion of luteinising hormone and follicle stimulating hormone. The pulse frequency of gonadotrophin releasing hormone is controlled by multiple upstream endocrine and neural factors, with a higher frequency favouring secretion of luteinising hormone and a lower frequency favouring secretion of follicle stimulating hormone. In women with polycystic ovary syndrome, raised levels of luteinising hormone cause excess production of ovarian thecal androgens, whereas relative deficiency of follicle stimulating hormone causes follicular arrest, polycystic ovarian morphology, and oligo-ovulation.[4] The reduction in sex steroid feedback on release of gonadotrophin releasing hormone is thought to occur upstream of the hormone itself because gonadotrophin releasing hormone neurons do not have receptors for oestrogens or progesterone[13] (figure 1). KNDy neurons have an important role in this regard (figure 1).

Kisspeptins are a family of peptides encoded by the *KISS1* gene which act on the neuronal G protein coupled receptor KISS1R. *KISS1* encodes prepro-kisspeptin, which is cleaved to produce the biologically active peptides KP54, KP14, KP13, and KP10.[14] Two discrete neuronal populations exist: KNDy neurons in the infundibular nucleus function as the gonadotrophin releasing hormone pulse generator[15] and mediate negative feedback from oestradiol,[16] whereas a separate kisspeptin population located in the preoptic area mediates oestradiol positive feedback to produce the mid-cycle surge in luteinising hormone.[16 17] Kisspeptin neurons express sex steroid receptors (progesterone and oestrogen receptors) required for negative feedback on gonadotrophin releasing hormone pulsatility.[17 18] *KISS1* is also expressed in adipose tissue where it is regulated independently of hypothalamic *KISS1*.[19] Circulating levels of kisspeptin are higher in patients with polycystic ovary syndrome than in controls[20] and although the origin of this excess is not entirely clear, a raised pulse frequency of kisspeptin in women with oligomenorrhoea and polycystic ovary syndrome suggests a hypothalamic source.[21] Moreover, physiological coupling of kisspeptin and luteinising hormone pulsatility is lost in these women.[21] The exact mechanisms for these effects are unclear, with inconsistent data from preclinical models on the existence and direction of dysregulated gonadotrophin releasing hormone pulsatility mediated by kisspeptin.[22]

Neurokinin B and dynorphin are expressed by KNDy neurons and act in an autocrine and paracrine way to control release of kisspeptin (figure 1). Neurokinin B preferentially binds to the neurokinin 3 receptor (encoded by *TACR3*) to stimulate gonadotrophin releasing hormone pulsatility.[4 23] Unlike *KISS1* null mice, mice deficient in components of neurokinin B signalling can still generate surges in luteinising hormone and conceive, suggesting that compensatory pathways exist which contribute to the generation of kisspeptin and gonadotrophin releasing hormone pulses.[17 24 25] This milder effect of neurokinin B blockade might avoid excessive reduction in gonadotrophin releasing hormone pulsatility, making it an attractive target for treatment.[4] Dynorphin, which activates kappa opioid receptors on KNDy neurons to inhibit secretion of gonadotrophin releasing hormone,[22 26] has been shown to mediate progesterone negative feedback on gonadotrophin releasing hormone neurons in sheep[27] and humans.[22 28]

Neuronal activity of gonadotrophin releasing hormone is also regulated by other substances, including γ-aminobutyric acid (GABA) and anti-müllerian hormone, both of which stimulate gonadotrophin releasing hormone neurons directly. GABA exerts an excitatory effect on gonadotrophin releasing hormone neurons through $GABA_A$ receptors, and GABA levels in cerebrospinal fluid can be raised in patients with polycystic ovary syndrome.[29] Anti-müllerian hormone is secreted by ovarian

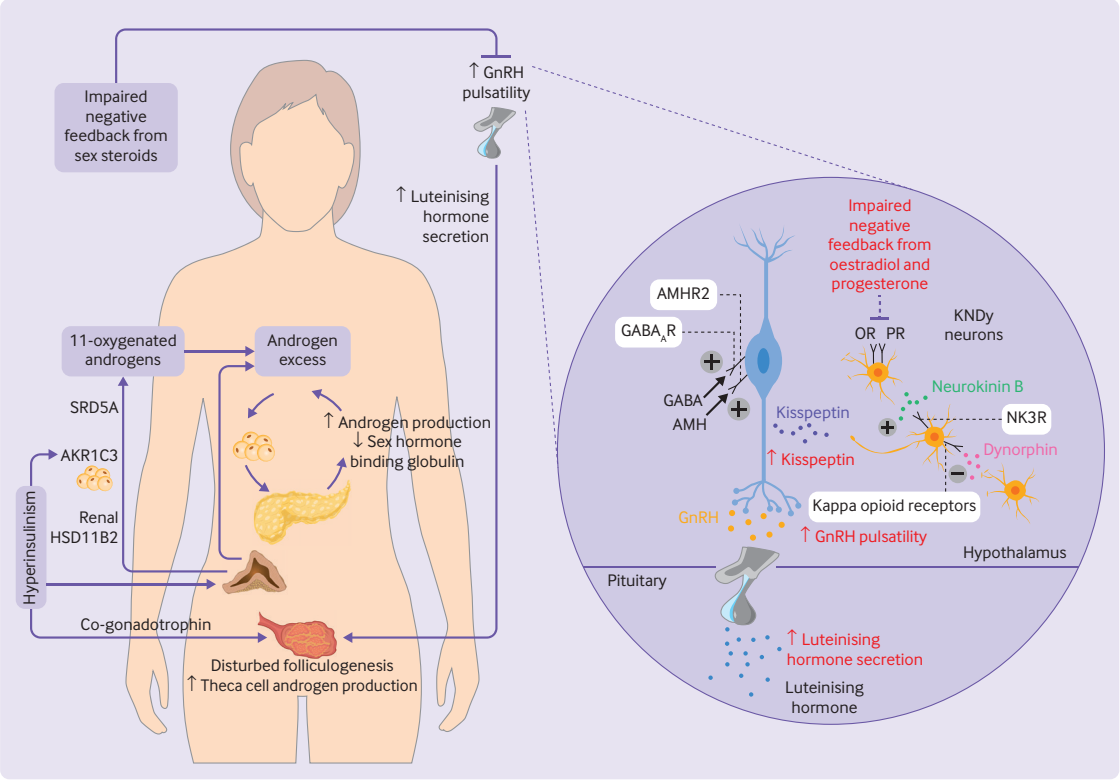

Figure 1 | Pathophysiology and neuroendocrine disruption of the hypothalamo-pituitary-gonadal axis in polycystic ovary syndrome. (Left) Increased pulsatility of gonadotrophin releasing hormone (GnRH) causes increased secretion of luteinising hormone, consequent disrupted folliculogenesis, and increased production of ovarian androgens. Adrenal androgens are also increased, including 11-oxygenated androgens which are activated peripherally by renal 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2) and aldo-keto reductase 1C3 (AKR1C3) in adipocytes. Steroid-5α-reductase (SRD5A) converts 11-ketotestosterone to 11-ketodihydrotestosterone. Excess levels of androgens stimulate deposition of abdominal adipose tissue which subsequently increases insulin resistance and hyperinsulinism. Hyperinsulinism stimulates AKR1C3 activity, increases androgen production from the ovaries (by its action as a co-gonadotrophin) and adrenal cortex, reduces production of hepatic sex hormone binding globulin, and inhibits progesterone mediated negative feedback onto GnRH neurons, worsening androgen excess in a vicious cycle. (Right) Kisspeptin, neurokinin B, and dynorphin A neurons (KNDy neurons) act in a paracrine and autocrine way to regulate release of kisspeptin onto GnRH neurons and consequent GnRH pulsatility. Neurokinin B binds to neurokinin 3 receptors (NK3R) to stimulate release of kisspeptin whereas dynorphin binds to kappa opioid receptors to inhibit kisspeptin release. γ-aminobutyric acid (GABA) and anti-müllerian hormone (AMH) bind to GABA$_A$ receptors (GABA$_A$R) and AMH receptor type 2 (AMHR2), respectively, to stimulate GnRH pulsatility. Impaired negative feedback from oestradiol and progesterone is seen at the level of the hypothalamus. Neuroendocrine abnormalities in the control of these components are shown in red. OR=oestrogen receptor; PR=progesterone receptor

granulosa cells, where raised levels in women with polycystic ovary syndrome disrupt folliculogenesis and ovulation.[30] Anti-müllerian hormone might also have neuroendocrine effects: 50% of gonadotrophin releasing hormone neurons in mice and humans express anti-müllerian hormone receptor type 2,[31] with studies implicating anti-müllerian hormone in neuronal migration of gonadotrophin releasing hormone,[32] gonadotrophin releasing hormone pulsatility, and secretion of luteinising hormone.[30]

Classical pathway of androgen synthesis

High levels of androgens is a primary defect in polycystic ovary syndrome. Cholesterol is converted to androgens by a cascade of enzymes common to all steroid producing organs, with tissue specific variations resulting in different steroid hormone profiles.[33] In polycystic ovary syndrome, increased production of ovarian androgens by the classical pathway is driven by increased secretion of pituitary luteinising hormone, the action of insulin as a co-gonadotrophin, and increased thecal cell hypersensitivity to luteinising hormone.[34–36] Figure 2 summarises the classical pathway of steroidogenesis. Through a sequence of reactions, cholesterol is converted to dehydroepiandrosterone, which is then converted to androstenedione by 3β-hydroxysteroid dehydrogenase type II and subsequently to testosterone by aldo-keto reductase type 1C3 (AKR1C3).[35]

Increased activity of ovarian 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which converts

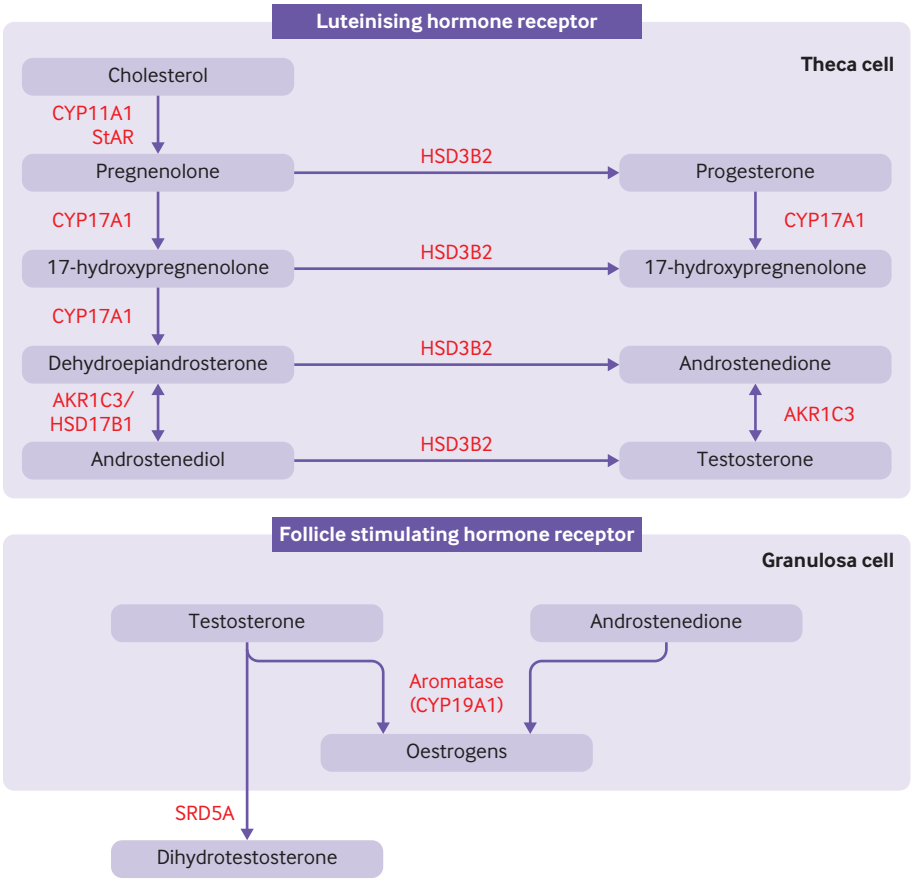

Figure 2 | Classical pathway of androgen synthesis. Luteinising hormone stimulates the classical pathway of androgen synthesis in ovarian theca cells. Cholesterol is transported to the inner mitochrondrial membrane by steroidogenic acute regulatory protein (StAR). A cleavage system of the cytochrome P450 enzyme, CYP11A1, ferrodoxin, and ferrodoxin reductase converts cholesterol to pregnenolone. Expression of CYP11A1 is stimulated by activation of the luteinising hormone receptor. Pregnenolone is transported to smooth endoplasmic reticulum where it is converted to 17-hydroxypregnenolone and subsequently to dehydroepiandrosterone by the 17-hydroxylase and 17,20-lyase subunit of the CYP17A1 enzyme, respectively. Dehydroepiandrosterone is then converted to androstenedione or androstenediol and subsequently to testosterone by a combination of 3β-hydroxysteroid dehydrogenase type II (HSD3B2) and aldo-keto reductase type 1C3 (AKR1C3). 17β-hydroxysteroid dehydrogenase 1 (HSD17B1) also catalyses the conversion of dehydroepiandrosterone to androstenediol. HSD3B2 converts pregnenolone and 17-hydroxypregnenolone to progesterone and 17-hydroxyprogesterone, respectively, which are substrates for a back door alternative pathway of androgen synthesis. Androstenedione and testosterone diffuse into granulosa cells where they are converted to oestrogens by the action of aromatase (CYP19A1), under the control of follicle stimulating hormone receptor activation. Testosterone can be converted to dihydrotestosterone by steroid 5α-reductase (SRD5A) in peripheral tissues

inactive cortisone to active cortisol, might also have a role in the pathogenesis of polycystic ovary syndrome.[37] Overexpression of ovarian 11β-HSD1 in rats caused polycystic ovarian morphology, oestrous cycle, and reproductive hormone abnormalities.[37] Although 11β-HSD1 is widely expressed, dysregulation seems to be tissue specific, because hepatic 11β-HSD1 activity is impaired and expression of 11β-HSD1 in subcutaneous adipose tissue is increased in patients with polycystic ovary syndrome.[38] Raised circulating levels and ovarian expression of vascular endothelial growth factor also contribute to the hypervascular, hyperplastic appearance of the ovarian stroma and theca interna in polycystic ovary syndrome, and might contribute to increased ovarian androgen synthesis.[39]

Androgen synthesis in adrenal glands and peripheral tissues

Polycystic ovary syndrome was previously thought to be primarily a disease of excess production of androgens in the ovaries, but the adrenal glands and peripheral tissues are now considered important sources of androgens in patients with polycystic ovary syndrome. Increased concentrations of dehydroepiandrosterone sulphate, an almost exclusive product of the adrenal cortex,[40] are apparent in 20-30% of patients with polycystic ovary syndrome.[41] This finding seems to be the result of increased secretory activity of the adrenal cortex because no change in pituitary responsiveness to corticotrophin releasing hormone or reduction in the minimal stimulatory dose of adrenocorticotropic hormone required for

adrenal hormone production is seen.[42] Changes in steroidogenesis, such as increased enzymatic activity of the 17-hydroxylase subunit of the cytochrome P450 enzyme, CYP17A1, might account for this hyper-responsiveness.[43]

Other adrenal androgens are also secreted in excess, including 11β-hydroxyandrostenedione and 11β-hydroxytestosterone.[5 44] The adrenal androgen 11β-hydroxyandrostenedione is abundant and was previously thought to have little physiological importance because of its weak androgenic activity. Recent studies, however, have shown that 11β-hydroxyandrostenedione can be metabolised to 11-ketotestosterone and 11-ketodihydrotestosterone, termed 11-oxygenated androgens, because of the presence of an oxygen atom on carbon 11.[45] Both 11-ketotestosterone and 11-ketodihydrotestosterone bind to androgen receptors with similar affinity and potency to testosterone and dihydrotestosterone.[46 47] Mass spectrometry analyses have shown that 11-oxygenated androgens are the dominant circulating androgens in women with polycystic ovary syndrome and correlate substantially with markers of metabolic risk.[5] The synthesis of 11-oxygenated androgens is reliant on the peripheral activation of adrenal derived androgens (figure 3). 11β-hydroxysteroid dehydrogenase type 2 is an enzyme expressed by the kidney that converts 11β-hydroxyandrostenedione to 11-ketoandrostenedione, and 11β-hydroxytestosterone to 11-ketotestosterone.[45] Adipose tissue also has enzymes responsible for potent androgen formation, however, and might represent the dominant source of circulating 11-oxygenated androgens.[45 48]

Expression of the androgen activating enzyme, AKR1C3, in subcutaneous adipose tissue is increased in women with polycystic ovary syndrome compared with matched controls.[6 49] Thus concentrations of

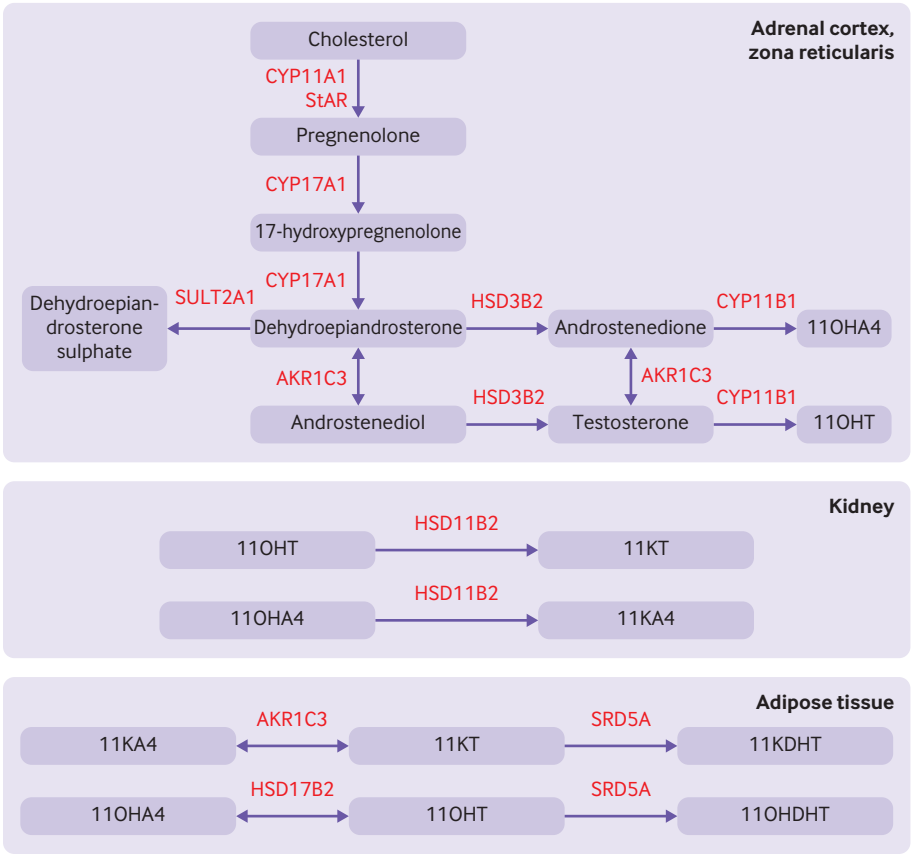

Figure 3 | Pathway for 11-oxygenated androgen synthesis, which begins in the adrenal cortex. Androstenedione and testosterone are produced by the classical pathway (figure 2). Dehydroepiandrosterone is diverted to downstream androgens or sulphonated to dehydroepiandrosterone sulphate by the sulphotransferase, SULT2A1. Androstenedione and testosterone are hydroxylated by 11β-hydroxylase (CYP11B) to produce abundant 11β-hydroxyandrostenedione (11OHA4) and smaller amounts of 11β-hydroxytestosterone (11OHT). Renal 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2) converts 11OHT to 11-ketotestosterone (11KT) and 11OHA4 to 11-ketoandrostenedione (11KA4). In adipose tissue, 11KA4 is metabolised to 11KT and 11-ketodihydrotestosterone (11DHKT) by aldo-keto reductase type 1C3 (AKR1C3) and steroid-5α-reductase (SRD5A), respectively. 11OHA4 is metabolised to 11OHT and 11β-hydroxydihydrotestosterone (11OHDHT) by 17β-hydroxysteroid dehydrogenase 2 (HSD17B2) and SRD5A, respectively. 11KT and 11KDHT are potent agonists of the androgen receptor whereas 11OHT and 11OHDHT have milder potency. StAR=steroidogenic acute regulatory protein; HSD3B2=3β-hydroxysteroid dehydrogenase type II; CYP11A1, CYP17A1, CYP11B1=cytochrome P450 enzymes

androgens in adipose tissue are increased in women with polycystic ovary syndrome, accompanied by inhibition of lipolysis and increased de novo lipogenesis.[6] These observations suggest that inhibition of AKR1C3 might be an attractive therapeutic target in patients with polycystic ovary syndrome.

Hyperinsulinism

Insulin resistance, and the consequent hyperinsulinism, have an important role in driving androgen synthesis in many endocrine tissues. Insulin acts as a co-gonadotrophin in the ovaries,[36] impairs progesterone mediated inhibition of the gonadotrophin releasing hormone pulse generator,[50] and facilitates synthesis of androgens in the adrenal glands by increasing adrenocorticotropic hormone stimulated steroidogenesis.[51] AKR1C3 expression and activity in adipocytes is increased by insulin, contributing to increased synthesis of androgens in adipocytes in polycystic ovary syndrome.[52] Insulin also inhibits sex hormone binding globulin, facilitating hyperandrogenism by increasing the percentage of free biologically active androgens.[53] Excess production of androgens then stimulates hyperinsulinism, leading to a vicious cycle between androgen and insulin excess.[7 54] Several studies have also implicated hyperandrogenism in the accumulation of abdominal and visceral adipose tissue in polycystic ovary syndrome[55 56]; this hyperandrogenism further drives insulin resistance and consequent production of androgens (figure 1).

In common with hyperandrogenism, insulin resistance is not a universal feature of polycystic ovary syndrome, although a systematic review of hyperinsulinaemic-euglycaemic clamp studies of 1224 women with polycystic ovary syndrome and 741 controls showed that insulin sensitivity was lower in women with polycystic ovary syndrome than in controls (mean effect size −27%, 99% confidence interval −21 to −33).[57] Studies exploring steroid metabolomics in patients with polycystic ovary syndrome might give more information. One such cross sectional study (n=488) combining machine learning with mass spectrometry multisteroid profiling has identified three distinct groups of patients based on the predominant source of androgens.[58] These subgroups have distinct steroid metabolomes and risk of metabolic complications: a gonadal derived classical androgen excess group, an adrenal derived androgen excess group (comprising 11-oxygenated androgens), and a group with comparably mild androgen excess.[58] The adrenal derived androgen group had the highest rates of hirsutism, insulin resistance, and type 2 diabetes. These insights challenge our understanding of polycystic ovary syndrome as one entity and might prompt a reconsideration of the classification of the disease based on the metabolomic signature.

Changes in adipocyte structure and function

Changes in white adipose tissue morphology and function is seen in women with polycystic ovary syndrome, including enlarged adipocytes, reduced lipoprotein lipase activity,[59] and increased secretion of proinflammatory cytokines.[60] The function of brown adipose tissue might also be disrupted because women with polycystic ovary syndrome showed reduced postprandial thermogenesis compared with controls matched for body mass index.[61] This defect could be driven by androgen excess, because prenatally androgenised sheep have reduced postprandial thermogenesis in adulthood,[62] accompanied by reduced adipose expression of thermogenic uncoupling proteins and sympathetic activity. Adolescent prenatally androgenised sheep also showed reduced hepatic expression and circulating levels of fibroblast growth factor 21,[63] a hormone that regulates adipocyte function, insulin sensitivity, and energy balance. Targeting expression of fibroblast growth factor 21 during an appropriate period in development might be a therapeutic option.

Gut microbiota and bile acid metabolism

Recent studies have implicated changes in the gut microbiome in the pathogenesis of polycystic ovary syndrome. Women with polycystic ovary syndrome have higher intestinal levels of *Bacteroides vulgatus* and lower levels of glycodeoxycholic acid and tauroursodeoxycholic acid.[64] Oral gavage of wild-type mice with faecal microbiota from individuals with polycystic ovary syndrome or pure *B vulgatus* caused insulin resistance, changes in bile acid metabolism, reduced secretion of interleukin 22, and disrupted oestrous cycle and ovarian morphology.[64] Administration of interleukin 22 or glycodeoxycholic acid to mice treated with *B vulgatus* improved insulin sensitivity, testosterone levels, and oestrous cycles. Hence modifying the gut microbiota or bile acid metabolism, increasing levels of interleukin 22, or a combination of these actions, might be therapeutically valuable in polycystic ovary syndrome.[64]

Insights from genome-wide association studies

Genome-wide association studies have identified numerous susceptibility loci for polycystic ovary syndrome, including 11 in Han Chinese populations,[65 66] eight in European populations,[67 68] and eight in a Korean population.[69] Robust candidate susceptibility loci are near genes belonging to metabolic (insulin receptor (INSR), insulin gene-variable number of tandem repeats (INS-VNTR), and DENN domain containing protein 1A (DENND1A))[70] and neuroendocrine (follicle stimulating hormone receptor, luteinising hormone receptor, and thyroid adenoma associated (THADA)) pathways.[70] Meta-analyses of genome-wide association studies have shown that the genetic architecture of polycystic ovary syndrome is consistent across different

diagnostic criteria and ethnic groups.[71 72] These observations indicate a shared ancestry for polycystic ovary syndrome and reinforce the importance of neuroendocrine and metabolic pathways in the pathogenesis of the disease.

Developmental programming

Genetic loci identified by genome-wide association studies currently account for only 10% of the known heritability (about 70%) of polycystic ovary syndrome,[73 74] suggesting other influences on the pathogenesis of the disease. Emerging evidence indicates that polycystic ovary syndrome might have its origins in utero, and thus could be subject to developmental programming and epigenetic modifications. Prenatal exposure to androgens in several preclinical models caused a permanent polycystic ovary syndrome-like phenotype postnatally.[75–77] A programming effect might also persist transgenerationally, because pregnant mice treated with dihydrotestosterone produced female offspring with polycystic ovary syndrome-like phenotypes from the first to the third generations of offspring.[78] Cautious interpretation is needed, however, because these models might not accurately reflect the human phenotype. Anti-müllerian hormone might also be involved in in utero programming: levels of anti-müllerian hormone increased significantly in pregnant women with polycystic ovary syndrome (P<0.001), and use of this hormone caused gonadotrophin releasing hormone neuronal hyperactivity and androgen excess in pregnant mice.[79] Epigenetic mechanisms might also be involved in mediating susceptibility to polycystic ovary syndrome, with differential methylation patterns and microRNA expression detected in adipose tissue and ovarian tissue of patients with polycystic ovary syndrome compared with controls.[80]

Health risks

Polycystic ovary syndrome is well established as a reproductive disorder associated with hyperandrogenism, and is the leading cause of oligomenorrhoea and amenorrhoea.[81] Patients with polycystic ovary syndrome are at increased risk of mental health disorders,[82 83] endometrial cancer,[84] and ovarian hyperstimulation syndrome after induction of ovulation.[85] Consistent with our understanding of the pathogenesis, however, polycystic ovary syndrome is also recognised as a metabolic disorder, with long term health risks, including hypertension, type 2 diabetes, dyslipidaemia, insulin resistance, and obesity.[1] These health risks could be associated with an increased risk of cardiovascular events[86] and several adverse pregnancy outcomes.[87] Although the reproductive aspects might diminish with age, metabolic features typically persist or can worsen.[88]

Therapeutic goals

Difficulty in losing weight, irregular menses, infertility, and excessive hair growth were the most important health problems reported by patients with polycystic ovary syndrome in an international survey.[2] These problems should therefore represent the main targets for therapeutic intervention, although priority setting partnerships are still needed to help focus research priorities. Existing drug treatments have not been licensed specifically for polycystic ovary syndrome and are used off-label to target symptoms. Also, previous studies have not emphasised health related quality of life measures when evaluating response to treatment. An ideal treatment for polycystic ovary syndrome should look at the health risks, reduce key processes in the pathogenesis of the disease, and be responsive to the symptom profile and needs of the individual. Where relevant, treatments should reduce clinical and biochemical hyperandrogenism, restore ovulatory cycles and fertility, normalise the length of the menstrual cycle, improve insulin sensitivity, reduce weight and cardiometabolic risk, and improve condition specific quality of life.

Existing treatments

Non-pharmacological interventions

International guidelines highlight the importance of modifications to lifestyle in the management of the disease.[3] Changes in lifestyle can improve fasting insulin levels and anthropometric outcomes, although benefits on hyperandrogenism are modest[89] and adherence is often difficult to sustain in clinical practice. Data on reproductive benefits are limited,[90] although a recent small randomised controlled trial of 68 women with polycystic ovary syndrome showed that a behavioural modification programme improved menstrual regularity compared with a minimal intervention group.[91] Laser treatment might have a role in the treatment of facial hirsutism, although further trials are needed to confirm the benefits on quality of life and cost effectiveness.[3]

Contraceptive pill

In women not attempting to conceive, combined contraceptive pills are first line treatments for menstrual irregularity and hyperandrogenism.[3] The oestrogen component increases sex hormone binding globulin, thus reducing free testosterone and improving hyperandrogenism. Because this stimulatory effect on hepatic production of proteins also causes hypercoagulability, ethinyloestradiol based contraceptive pills containing the lowest effective dose of oestrogen (eg, 20-30 µg of ethinyloestradiol) are recommended.[3] Combined contraceptive pills containing newer, more physiological, oestrogenic compounds have recently been developed, and might have a lower risk of venous thromboembolism than ethinyloestradiol.[92] The progestogen

component reduces ovarian androgen production by inhibiting secretion of luteinising hormone and protects the endometrium from hyperplasia.[93] Combined contraceptive pills containing androgenic progestogens, such as norethisterone, should be avoided because of the potential to aggravate hyperandrogenic symptoms. Furthermore, ethinyloestradiol based contraceptive pills containing cyproterone acetate, the most potent anti-androgenic progestogen, are not currently recommended as first line treatment because of the increased risk of venous thromboembolism.[3] A recent systematic review of 19 randomised controlled trials, however, concluded that the ethinyloestradiol-cyproterone acetate combination improved serum testosterone (mean difference 0.38 nmol/L, 95% confidence interval 0.33 to 0.43) and hirsutism compared with conventional combined contraceptive pills.[94] Thus combinations of cyproterone acetate and newer oestrogenic compounds might have the potential to improve hyperandrogenism in patients with polycystic ovary syndrome without the added risk of venous thromboembolism.

Anti-androgen agents

Currently available anti-androgen agents act by blocking androgen receptors (cyproterone acetate, spironolactone, and flutamide) or reducing production of androgens (finasteride and dutasteride). Guidance on specific preparations or doses in polycystic ovary syndrome is necessarily vague, because studies on these agents are few in number and small scale.[3] Furthermore, although targeting excess production of androgens might be crucial to improved patient outcomes, the use of currently available anti-androgen drugs is limited by side effects. All anti-androgen drugs carry a risk of feminisation of a male fetus and therefore use must be restricted to patients with adequate contraception in place.[3]

Insulin sensitisers

Metformin modulates hepatic insulin sensitivity and glucose production by activating AMP activated protein kinase and AMP activated protein kinase independent pathways. More recently, metformin has also been shown to mediate its antiglycaemic effects by actions on the gastrointestinal tract and the gut microbiome.[95] Metformin is used to manage weight and metabolic outcomes in adult women with polycystic ovary syndrome with a body mass index ≥25.[3] Metformin might also improve ovulation and live birth rates but is less effective than clomifene citrate or letrozole.[3 96] Nevertheless, because of its wide availability and low cost, metformin could still be valuable in improving reproductive outcomes in women with polycystic ovary syndrome, especially in healthcare economies where access to assisted reproduction is limited.

Thiazolidinediones improve insulin sensitivity by activating nuclear peroxisome proliferator activated receptor γ. A meta-analysis of eight randomised controled trials concluded that thiazolidinediones reduce insulin and fasting glucose levels in polycystic ovary syndrome, but do not seem to affect hirsutism scores or serum levels of androgens.[97] Existing data on thiazolidinediones in polycystic ovary syndrome are limited. Thiazolidinediones are associated with intrauterine growth restriction in animal studies and weight gain in humans.[98] Thiazolidinediones are thus not recommended for use in polycystic ovary syndrome outside of the licensed indication in type 2 diabetes. Preliminary studies suggest that the insulin sensitiser inositol might improve glycaemic control[99] and new international guidelines recommend shared decision making on using inositol for its potential metabolic benefits in polycystic ovary syndrome. Specific doses, forms, or combinations of the substance, however, cannot be recommended because of a lack of high quality evidence.[3]

New therapeutic targets

Kisspeptin based treatment

Kisspeptin has a major role as a regulator of the hypothalamic-pituitary-gonadal axis, and therefore extensive efforts have been made in investigating the effects of kisspeptin based treatment in women with polycystic ovary syndrome and in other disorders of reproduction. KP54 and KP10 are the most studied native kisspeptins in humans and have been investigated for their potential role in optimising oocyte maturation in patients undergoing in vitro fertilisation.[100 101] Although the two compounds bind to KISS1R with similar affinity, KP54 has a longer serum half-life than KP10 and a more profound effect on secretion of luteinising hormone.[102] A bolus dose of KP54 induces oocyte maturation in patients with polycystic ovary syndrome without causing clinically significant ovarian hyperstimulation syndrome.[100 101] Administration of a subcutaneous bolus injection of native kisspeptin is safe and well tolerated[103] and also results in higher expression of gonadotrophin receptors (follicle stimulating hormone receptor and luteinising hormone receptor) and steroidogenic enzymes (including aromatase CYP19A1, steroidogenic acute regulatory protein, and 3β-hydroxysteroid dehydrogenase type II) in ovarian granulosa cells, potentially promoting an ovarian environment favouring progesterone synthesis and ovarian implantation.[104]

Use of KP54 as an ovulation induction agent, however, might be limited by tachyphylaxis.[105] Because KP54 preferentially stimulates secretion of luteinising hormone over follicle stimulating hormone,[106] concerns also exist that long term administration of kisspeptin might exacerbate pre-existing deficiency of follicle stimulating hormone in polycystic ovary syndrome.[4] Nevertheless, KP54

effectively induced ovulation in neonatally androgenised rats but not in prenatal androgenisation or post-weaning androgenisation models.[107] Simultaneous increases in luteinising hormone and follicle stimulating hormone were seen after KP54 use in the neonatal androgenisation model, suggesting that ovulation induced by kisspeptin is linked to its ability to stimulate increases in both luteinising hormone and follicle stimulating hormone.[107] In a first-in-woman pilot study of 12 patients with polycystic ovary syndrome, twice daily use of KP54 over three weeks significantly increased levels of luteinising hormone (P=0.04) and oestradiol (P=0.03) but not follicle stimulating hormone or inhibin B.[107] Two of the 12 women developed a dominant follicle with subsequent ovulation. Hence long term administration of KP54 might be suitable for follicular maturation in a subset of patients with polycystic ovary syndrome, but more studies are needed to identify the patient characteristics that predict response to treatment.

KISS1R agonists are currently in development with modifications that increase potency and are resistant to proteolytic degradation. KISS1R agonists might have a lower risk of tachyphylaxis because of their longer duration of action, allowing less frequent dosing. The KISS1R agonist, MVT-602, showed greater potency than KP54, increasing release of luteinising hormone in healthy women with a longer duration of gonadotrophin releasing hormone neuronal activation in vitro.[108] When tested in patients with polycystic ovary syndrome, MVT-602 increased luteinising hormone with a similar amplitude but greater duration than KP54 in healthy women (area under the curve of luteinising hormone exposure 171.30 *v* 38.5 IU×h/L), similar to the natural mid-cycle surge in luteinising hormone.[108] These findings warrant further investigation in polycystic ovary syndrome and in other female reproductive disorders.

Paradoxically, kisspeptin receptor antagonists have also been suggested as therapeutic agents in polycystic ovary syndrome based on their potential to normalise hypersecretion of luteinising hormone, restore folliculogenesis and ovulation, and improve ovarian hyperandrogenism.[109] Existing KISS1R antagonists, such as P234 and P271, have inconsistent effects on kisspeptin induced stimulation of gonadotrophin releasing hormone-luteinising hormone across species.[110 111] Compound 15a is a small molecular KISS1R antagonist with antagonistic activity at the receptor and good permeability of the blood-brain barrier in rats.[112] KISS1R antagonists have yet to be tested in humans, however, and concerns exist that these agents will overly suppress secretion of luteinising hormone and stop ovulation.[4]

Neurokinin 3 receptor antagonists

Inhibition of the neurokinin 3 receptor is believed to cause a tempered inhibition of gonadotrophin releasing hormone pulsatility without excessive reduction because of the presence of compensatory pathways.[4 25] MLE4901 (also named AZD4901) had promising effects on levels of reproductive hormones in 65 women with polycystic ovary syndrome in a phase 2 randomised controlled trial.[113] After seven days of treatment with MLE4901 80 mg/day, the area under the luteinising hormone curve was reduced by 52.0% (95% confidence interval 29.6% to 67.3%), total testosterone concentration was reduced by 28.7% (13.9% to 40.9%), and luteinising hormone pulses were reduced by 3.55 pulses/8 hours (2.0 to 5.1).[113] MLE4901 was discontinued, however, because of increased levels of transaminases in some patients.[114 115] Hepatotoxicity is believed to be specific to MLE4901 and has not been reported with other neurokinin 3 receptor antagonists.[115]

In a phase 2 randomised controlled trial in 64 women with polycystic ovary syndrome, treatment with the neurokinin 3 receptor antagonist, fezolinetant, for 12 weeks at 60 mg or 180 mg, reduced levels of testosterone by 17% (95% confidence interval −28.7% to −4.6%) and 33% (−45.91% to −20.4%), respectively, compared with 1% (−8.8% to 11.7%) with placebo.[116] Levels of luteinising hormone but not follicle stimulating hormone were significantly reduced (P<0.001) in a dose dependent manner, reducing the ratio of luteinising hormone to follicle stimulating hormone.

Preclinical studies have also highlighted the potential metabolic benefits of neurokinin 3 receptor antagonists. In a dihydrotestosterone induced mouse model of polycystic ovary syndrome, treatment with neurokinin 3 receptor antagonists decreased body weight and adiposity.[117] No changes in food intake or energy expenditure were seen, although an increased respiratory exchange ratio suggested that neurokinin 3 receptor antagonists cause a shift to a carbohydrate predominant utilisation of fuel.[117] These promising observations suggest that neurokinin 3 receptor antagonists fulfil many of the properties of an ideal treatment for polycystic ovary syndrome, and further clinical trials are awaited with interest.

Dynorphin, γ-aminobutyric acid, and anti-müllerian hormone based treatment

When dynorphin binds to kappa opioid receptors, release of kisspeptin onto gonadotrophin releasing hormone neurons is inhibited, and therefore selective kappa receptor agonists with a central action might reduce gonadotrophin releasing hormone pulsatility.[4] A new generation of peripherally selective kappa receptor agonists have been developed that might access brain regions, including the infundibular nucleus, by fenestrated capillaries in the median eminence.[118] The kappa receptor agonist,

difelikefalin, does not seem to cause the centrally mediated side effects of dysphoria and sedation of previous kappa receptor agonists, and has recently been approved in the US for the treatment of moderate-to-severe pruritus in adults undergoing haemodialysis.[119 120] In a prenatally androgenised mouse model of polycystic ovary syndrome, difelikefalin reduced serum levels of luteinising hormone and testosterone, restored oestrous cyclicity and ovulation, and reduced overexpression of *KISS1* mRNA in the hypothalamic preoptic area.[121]

Centrally acting $GABA_A$ antagonists might also benefit patients with polycystic ovary syndrome. Although weight gain could in part explain the increased incidence of polycystic ovary syndrome in women receiving sodium valproate, this drug also increases levels of $GABA_A$ in the central nervous system.[122] In contrast, peripheral levels of GABA are reduced in patients with polycystic ovary syndrome,[123] and enteral administration of $GABA_A$ reduced body mass index and levels of testosterone in a letrozole induced polycystic ovary syndrome model.[124] Antagonism of the anti-müllerian hormone pathway might also be therapeutically useful; recent insights into the structural basis for binding of anti-müllerian hormone to anti-müllerian hormone receptor type 2 could facilitate the rational design of anti-müllerian hormone antagonists.[125]

Targeting key enzymes in steroidogenesis

AKR1C3 functions as the gatekeeper in classical and 11-oxygenated androgen synthesis by mediating enzymatic conversion of androstenedione to testosterone and 11-ketoandrostenedione to 11-ketotestosterone.[6] Various AKR1C3 inhibitors have been developed, with mixed results for their antineoplastic effects and ability to inhibit prostaglandin F synthase activity in castration resistant prostate cancer, acute myeloid leukaemia, and oestrogen receptor positive breast cancers.[126–128] Although steroidal based inhibitors of AKR1C3 are in development, the therapeutic potential in preclinical models of polycystic ovary syndrome has not been examined.[129] Selective inhibition of 11β-HSD1 with BVT.2733 in a rodent model of polycystic ovary syndrome improved insulin resistance, reproductive hormone dysfunction, and polycystic ovarian morphology.[37] These observations are encouraging but further preclinical work is needed before the potential therapeutic benefits of AKR1C3 and 11β-HSD1 inhibitors can be tested in patients.

Glucagon-like peptide 1 inhibitors

Glucagon-like peptide 1 (GLP-1) receptor agonists increase glucose dependent insulin secretion, suppress secretion of glucagon, and increase peripheral insulin sensitivity by weight loss (by stimulation of satiety) and suppression of inflammation in adipose tissue.[130] Although these properties might be therapeutically attractive in patients with polycystic ovary syndrome, previous randomised controlled trials were largely small, single centre, and of limited duration.[131] Nevertheless, in a network meta-analysis of 941 women with polycystic ovary syndrome and overweight or obesity, liraglutide was superior to metformin (mean difference −3.82, 95% confidence interval −4.44 to −3.20) and orlistat (−1.95, −3.74 to −0.16) in reducing body weight.[132] Some studies showed that GLP-1 receptor agonists improved menstrual regularity or frequency, and that these improvements in menstrual frequency correlated with reduction in body weight.[133 134] GLP-1 receptor agonists have also been shown to lower levels of androgens[133 135] and improve markers of cardiovascular risk.[136 137] A meta-analysis of eight randomised controlled trials concluded that GLP-1 agonists were more effective than metformin in improving homeostasis model assessment-insulin resistance (standard mean difference −0.40, 95% confidence interval −0.74 to −0.06), abdominal circumference (−0.45, −0.89 to −0.00), and body mass index (−1.02, −1.85 to −0.19), but not in improving menstrual frequency (0.15, −0.24 to 0.54) or serum levels of testosterone (0.64, −0.08 to 1.35).[138] Newer longer acting GLP-1 analogues, such as semaglutide or dulaglutide,[139 140] or dual GLP-1-glucose dependent insulinotropic polypeptide agonists, such as tirzepatide,[141] could provide more therapeutic opportunities, with the potential benefits of greater effects on weight loss, longer duration of action, and improved adherence. Semaglutide, the only GLP-1 agonist currently available in an oral formulation, is being investigated in a clinical trial in adolescent girls with polycystic ovary syndrome and obesity (Treating PCOS With Semaglutide vs Active Lifestyle Intervention (TEAL), NCT03919929). More adequately powered trials with a focus on core outcomes of polycystic ovary syndrome[142] are needed to establish whether these new drugs have a role in clinical management.

Sodium-glucose co-transporter inhibitors

Sodium-glucose co-transporter 2 inhibitors reduce reabsorption of glucose in the proximal convoluted tubules of the kidney, promoting excretion of urinary glucose, and also reduce weight and cardiovascular events in other populations.[143] Current data in patients with polycystic ovary syndrome are limited to four small randomised controlled trials.[144–148] Canagliflozin showed greater improvements in body mass index (P=0.006), basal metabolic rate (P=0.02), and fat mass (P=0.02) than metformin in women with polycystic ovary syndrome, but not in hormonal or metabolic parameters.[144] In overweight and obese patients with polycystic ovary syndrome, combined canagliflozin-metformin treatment for three months produced greater reductions than metformin monotherapy in total testosterone (−0.33 *v* −0.18 ng/mL, P=0.02), area under the curve for glucose (−158.00 *v*

Table 1 | Emerging drug treatments for polycystic ovary syndrome

Therapeutic class (references)	Drug	Phase of testing	Outcome measures	Main findings	Potential clinical benefits	Adverse effects (observed or potential)
Native kisspeptin[100 101 104 105 107]	KP54, KP10	Phase 1-2	Phase 1 and 2 clinical studies: Oocyte maturation (in women at high risk of ovarian hyperstimulation syndrome, including polycystic ovary syndrome)	KP54 triggered oocyte maturation without causing ovarian hyperstimulation syndrome. A second dose of KP54 improved oocyte yield	Oocyte maturation with reduced risk of ovarian hyperstimulation syndrome. Promotion of progesterone rich ovarian environment favouring ovarian implantation	Tachyphylaxis after repeated and long term dosing. Follicle stimulating hormone deficiency in polycystic ovary syndrome
			Pilot study in 12 women with polycystic ovary syndrome: Hormonal (gonadotrophin, oestradiol, inhibin B) and ovulatory responses to repeated KP54 administration	Increases in luteinising hormone and oestradiol but not follicle stimulating hormone or inhibin B. Development of a dominant follicle and subsequent ovulation in 2 of 12 women		
			In women with infertility undergoing in vitro fertilisation: Changes in gene expression in granulosa cells from women with infertility (most of whom had polycystic ovary syndrome)	Compared with human chorionic gonadotropin or gonadotrophin releasing hormone agonists, KP54 increased expression of gonadotropin receptors (follicle stimulating hormone receptor and luteinising hormone receptor) and steroidogenic enzymes (including aromatase CYP19A1, StAR, and HSD3B2) in ovarian granulosa cells		
KP10 analogues[108]	MVT-602 (TAK-448)	Phase 1	Pharmacokinetic and pharmacodynamic properties of MVT-602	Compared with KP54, MVT-602 increased luteinising hormone with similar amplitude but later peak, resulting in greater AUC of luteinising hormone exposure	Oocyte maturation with less frequent dosing than native kisspeptins	No serious adverse effects identified so far
KISS1R antagonist[110 111]	P234, P271, P354, P356, compound 15a	Preclinical	Basal and kisspeptin stimulated secretion of luteinising hormone	In female dogs, P234, P271, P354, and P356 did not affect basal or kisspeptin stimulated luteinising hormone secretion. P234 inhibited gonadotrophin releasing hormone neuron firing in mice and inhibited pulsatile gonadotrophin releasing hormone secretion in female monkeys. P234 inhibited kisspeptin stimulated luteinising hormone secretion in rats and mice	Improvement in ovulatory dysfunction and fertility. Improvement in biochemical and clinical hyperandrogenism	Oversuppression of luteinising hormone secretion leading to anovulation
Neurokinin 3 receptor antagonist[116 117 150]	Fezolinetant	Phase 2a	Fezolinetant *v* placebo: Change in total testosterone. Change in gonadotrophins, oestradiol, progesterone, anti-müllerian hormone, ovarian function and volume	Reduction in total testosterone. Reduction in luteinising hormone, reduction in luteinising hormone:follicle stimulating hormone ratio	Improvement in biochemical and clinical hyperandrogenism. Improvement in ovulatory dysfunction and fertility. Improvement in body weight and composition. Improvement in insulin sensitivity	Thrombophlebitis, headache, and gastrointestinal symptoms
			Dihydrotestosterone mouse model: Oestrous cycle regularity. Ovarian follicle count. Adipocyte morphology and adipose tissue mass. Serum adiponectin, leptin, cholesterol, triglyceride, fasting blood glucose levels. Food intake, energy expenditure, locomotor activity (metabolic cage study). Glucose homeostasis	Reduction in body weight. Reduction in inguinal, mesenteric, parametrial, and retroperitoneal fat pad weights. Reversal of adipocyte hypertrophy. Increased respiratory exchange ratio. Improvement in glucose tolerance		

Continued

Table 1 Continued

Therapeutic class (references)	Drug	Phase of testing	Outcome measures	Main findings	Potential clinical benefits	Adverse effects (observed or potential)
Opioid receptor agonists[119 121]	Difelikefalin	Preclinical	Prenatally androgenised mouse model: Oestrous cycle regularity. Hypothalamic *KISS1* expression. Luteinising hormone basal and peak levels, luteinising hormone pulse frequency. Testosterone levels	Oestrous cycle reversed to normal state. *KISS1* expression normalised in arcuate nucleus. Reduction in luteinising hormone pulse magnitude. Reduction of testosterone levels	Improvement in ovulatory dysfunction and fertility. Improvement in biochemical and clinical hyperandrogenism	Diarrhoea, dizziness, and vomiting
11β-HSD1 inhibitors[37]	BVT.2733	Preclinical	DHEA rodent model: Insulin sensitivity. Ovulatory function	Improvements in insulin resistance, ovulatory dysfunction, reproductive hormone dysfunction, and polycystic ovarian morphology	Improvement in insulin sensitivity. Improvement in ovulatory dysfunction and fertility	Yet to be tested in humans
GLP-1 agonists*[132–140]	Exenatide, liraglutide, dulaglutide, semaglutide	Phase 2-3	Systematic review of GLP-1 agonists *v* metformin: Changes in body weight and anthropometric parameters. Insulin sensitivity	GLP-1 agonists produced greater improvements in body weight, waist circumference, and insulin sensitivity	Improvement in weight and body composition. Improvement in cardiometabolic risk	Nausea, vomiting, and diarrhoea; safety in pregnancy unclear
			Liraglutide *v* placebo: Body weight. Ovarian morphology. Changes in menstrual pattern (bleeding ratio). Hyperandrogenism	Reduction in body weight. Improvement in bleeding ratio. Reduction in free androgen index, sex hormone binding globulin and free testosterone. Reduction in ovarian volume		
			Markers of cardiovascular risk: Serum endothelial markers (ICAM-1, P-selectin, E-selectin). Changes in endothelial function. Lipid levels	Exenatide improved serum markers of endothelial function without a change in endothelial function. Liraglutide improved thrombin generation test parameters. Liraglutide improved triglyceride levels and triglyceride:high density lipoprotein ratio		
SGLT2 inhibitors†[144 146 147]	Canagliflozin, dapagliflozin, empagliflozin	Clinical	Empagliflozin *v* placebo in humans: Changes in anthropometric parameters and body composition. Hormonal (total testosterone, androstenedione, sex hormone binding globulin, DHEAS) and metabolic (HOMA-IR, fasting lipids) parameters	Reduction in body weight, and hip and waist circumference. Reduction in fat mass. Reduction in basal metabolic rate. No change in hormonal and metabolic parameters	Improvement in weight and body composition. Improvement in cardiometabolic risk	Urinary tract infection and ketoacidosis
			Combination canagliflozin-metformin *v* metformin in humans: Anthropometric parameters, gonadotrophins, androgen levels, menstrual pattern, glucose and lipid homeostasis	Compared with metformin alone, combination canagliflozin-metformin produced greater reductions in total testosterone, AUC for glucose, and AUC ratio for insulin to glucose		
			Markers of cardiovascular risk in humans: Changes in serum endothelial markers (ICAM-1, E-selectin, VCAM-1, PECAM-1). Endothelial function	Empagliflozin reduced ICAM-1, E-selectin, and VCAM-1 but not PECAM-1, without a change in endothelial function		

Continued

Table 1 Continued

Therapeutic class (references)	Drug	Phase of testing	Outcome measures	Main findings	Potential clinical benefits	Adverse effects (observed or potential)
SGLT1-2 inhibitor[148]	Licogliflozin	Phase 2	Licogliflozin *v* placebo: Androgen levels. Insulin sensitivity (HOMA-IR). Hyperinsulinaemia (maximum (insulin), insulin AUC)	Reduction in androstenedione and DHEAS. Reduction in HOMA-IR and fasting glucose. Reduction in maximum (insulin) and insulin AUC. No change in free testosterone, total testosterone, sex hormone binding globulin, free androgen index, or DHEA	Improvement in insulin resistance. Reduction in androgen excess. Improvement in weight and cardiometabolic risk	Urinary tract infection, ketoacidosis, diarrhoea, and nausea

AUC=area under the curve; CYP19A1=cytochrome P450 family 19 subfamily A member 1; DHEA=dehydroepiandrosterone; DHEAS=dehydroepiandrosterone sulphate; GLP-1=glucagon-like peptide 1; HOMA-IR=homeostatic model assessment of insulin resistance; HSD3B2=3β-hydroxysteroid dehydrogenase; ICAM-1=intercellular adhesion molecule 1; *KISS1*=gene encoding kisspeptins in humans; KISS1R= KISS1 receptor; KP=kisspeptin; PECAM-1=platelet endothelial cell adhesion molecule; SGLT=sodium-glucose co-transporter; StAR=steroidogenic acute regulatory protein; VCAM-1=vascular cell adhesion molecule 1; 11β-HSD1=11β-hydroxysteroid dehydrogenase type 1.

*Clinical trial in progress: NCT03919929, Treating PCOS With Semaglutide vs Active Lifestyle Intervention (TEAL).

†Clinical trials in progress: NCT04213677, Dapagliflozin Efficacy and Action in PCOS (DEAP); NCT05200793, Efficacy of Empagliflozin or Linagliptin as an Alternative to Metformin for Treatment of Polycystic Ovary Syndrome.

2.63 mmol/L×min, P=0.02), and the ratio of the area under the curve for insulin and glucose (−2.86 *v* 0.51, P=0.02),[146] but no significant differences were found in menstrual frequency, body mass index, or homeostasis model assessment-insulin resistance between the treatment groups.[146]

Licogliflozin is a dual inhibitor of sodium-glucose co-transporter 1 (SGLT1) and 2 (SGLT2). Simultaneous SGLT1 and SGLT2 inhibition could provide more effective weight loss because SGLT1 inhibition alone stimulates intestinal secretion of GLP-1.[131] In a phase 2 randomised controlled trial of 29 patients, licogliflozin reduced levels of androstenedione by 19%, dehydroepiandrosterone sulphate by 24%, and hyperinsulinaemia by 70% in women with polycystic ovary syndrome.[148] The outcome of a recently completed randomised controlled trial of dapagliflozin on insulin resistance and serum levels of androgens in patients with polycystic ovary syndrome (Dapagliflozin Efficacy and Action in PCOS (DEAP), NCT04213677) is awaited with interest. Table 1 summarises the emerging treatments for polycystic ovary syndrome described in this review.

Guidelines

Guidelines on polycystic ovary syndrome vary in their methodological quality, approach to diagnosis, approach to screening for health risks, and recommendations for the use of drug treatments.[149] The 2023 update to the international polycystic ovary syndrome guidelines, which uses consensus methodology and clear grading systems for clinical recommendations, has now been released.[3] These evidence based guidelines were developed after consultation with international multidisciplinary and consumer bodies to support clinicians and patients in the diagnosis and management of polycystic ovary syndrome and reduce variation in care.

Conclusions

Polycystic ovary syndrome is a common reproductive and metabolic disorder resulting from polygenic and environmental influences. Key pathological changes include neuroendocrine dysregulation, excess production of androgens, insulin resistance, and changes in adipose tissue biology, with variation in dysfunction of these pathways contributing to differences in phenotypic expression and severity of the disease. Advances in genetic understanding, together with new techniques to assess the steroid metabolome, have identified new biological targets, challenged the perception of polycystic ovary syndrome as one entity, and could facilitate an individualised approach to long term cardiometabolic surveillance based on the metabolomic signature. These advances could, for the first time, enable the development of specific drug treatments for the disorder based on an improved understanding of the underlying pathophysiology. Well designed, multicentre, patient

centred clinical trials of neurokinin receptor antagonists, kisspeptin based treatments, and repurposed antidiabetic drugs are now needed to investigate new therapeutic options for polycystic ovary syndrome.

QUESTIONS FOR FUTURE RESEARCH

- ⇒ Should polycystic ovary syndrome be classified based on the steroid metabolomic signature, and specific treatments developed accordingly?
- ⇒ Does the steroid metabolome predict which patients are at increased risk of cardiometabolic disease?
- ⇒ Can reduction of 11-oxygenated androgens (eg, by inhibition of aldo-keto reductase type 1C3 (AKR1C3)) improve metabolic risk in patients with polycystic ovary syndrome?
- ⇒ Can later phase clinical trials of neurokinin 3 receptor antagonists show improvements in clinical hyperandrogenism and reproductive outcomes?

PATIENT INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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